UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAR 29 1991

MEMORANDUM

SUBJECT: Review of Dermal Sensitization Data on P91-391

FROM: James J. Murphy, Ph.D.
Toxicologist
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Oncology Branch
Health and Envioronmental
Review Division (TS-796)

TO: Raymond J. Kent, Ph.D.
Section Chief
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Chemical Review and Evaluation Branch
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THRU: Mary C. Henry, Ph.D.
Section Chief
General Toxicology Section
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Review Division (TS-796)

I have reviewed the test data on dermal sensitization caused by the premanufacturing-notice chemical, P91-391, reported by C.I.T. to S.N.P.E. (France). My report did not spell out what these initials represented. The report was in English, but the work seems to have been done in France. The report did not contain confidential business information.

Conclusion

Twenty Hartley-strain guinea pigs (ten of each sex) were tested by the Magnusson-Kligman protocol for dermal sensitization. Five guinea pigs of each sex served as vehicle controls. Test material P91-391 was a strong sensitizer. The vehicle was not an active irritant or sensitizer.

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Basis for Conclusion

Treated guinea pigs received intradermal injections of the test material at a concentration of 0.1% (which produced signs of irritation) on Day 1. Induction was completed a week later by topical administration of the test substance, occluded for 48 hours. No treatment was administered for 12 days, and then the guinea pigs were challenged by topical administration of a 25% solution of the test material (the maximum topical non-irritating concentration) for 24 hours. One male rat died on Day 10, before challenge, without showing signs of toxicity. This animal was apparently replaced, because they reported data on ten males.

Nineteen of the twenty test animals showed signs of sensitization after 24 hours; all twenty were positive for sensization after 48 hours. Erythema varied in intensity from well-developed to severe. Edema was not seen. Ten of the animals had scab formation after 24 hours; after 48 hours, thirteen had scabs. A couple of vehicle-control animals showed slight erythema during induction, but none reacted to challenge.

The testing laboratory considered the test material to be a "very strong, Level V" sensitizer. [Level V means the incidence of positive sensitization responses was 81-100%.]

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MEMORANDUM

SUBJECT: Addendum to Review of Dermal Sensitization Data on P91-391

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On March 29, 1991, I reviewed test data on P91-391 derived from the Magnusson-Kligman protocol. This test showed the PMN substance to be a strong sensitizer and irritant, so much so that I visited the CBIC to check on its chemical structure. There, in the initial submission, was the report of another test for dermal sensitization (using the Buehler protocol) that I had not seen before. The test material (0.5 ml, apparently applied neat) was not a sensitizer by the Buehler method.

Conclusion

P91-391 should be considered a skin sensitizer and irritant, although perhaps not so strong an irritant and sensitizer as I had indicated in my memorandum of March 29.

Basis for Conclusion

There was a marked to severe reaction in 100% of the guinea pigs tested by the Magnusson-Kligman method, but no reaction in any of the guinea pigs tested by the Buehler method. This was surprising. Although the Magnusson-Kligman method is widely considered to be the most sensitive of the seven or eight tests that the Agency recognizes for sensitization, and more sensitive than the Buehler method, the Buehler test is itself a sensitive one, and often shows substantial agreement with the Magnusson-Kligman method. Hardly ever does one see a 100% response with the Magnusson-Kligman test and zero with the Buehler.

When I saw a summary of the Buehler test (zero responders) as part of the Structure-Activity Team screening, I had been comfortable in calling P91-391 a non-sensitizer. At that time, I had not been shown the Magnusson-Kligman results.

It is difficult to say why the results of the Buehler and Magnusson-Kligman tests were so different. The Magnusson-Kligman protocol uses intradermal injection for induction and uses Freund's Complete Adjuvant, which tends to make the animal's skin more sensitive, whereas the Buehler test uses topical application and does not use Freund's adjuvant. There could be different rates of absorption. In the Buehler test, the material was applied neat, and neat material may be absorbed slower than in some solutions. The topical challenge phase of the Magnusson-Kligman test used a 10% solution of sodium lauryl sulfate in vaseline, which the Buehler test did not, and might have favored absorption, but vehicle-control guinea pigs did not respond during challenge.

In light of the 100% response on an established test, even if that test has been accused by some investigators of over-predicting, supported by findings of skin and eye irritation (with delayed corneal opacity on Days 10-22) on irritancy tests in rabbits, I believe it would be prudent to consider the PMN substance to be potentially irritating to skin and mucous membranes and sensitizing to skin.